Importance of Genomic Biomarker Validation in the Context of Pharmacogenomic Initiatives at the FDA

Janet Woodcock, M.D.
Deputy Commissioner for Operations
Food and Drug Administration
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Significant Progress in Recent Years

- Multiple public workshops
- Draft and final PG Guidance
- Functioning VGDS process
- Approval of PG diagnostics
- Efforts on drug-diagnostic codevelopment

Current Question: "Genomic Biomarker Validation"

- **A series of relatively confusing scientific, clinical, nomenclature and procedural issues**
- **Basic question: how do we get to genomic tests that are usable for regulatory decisions in drug development and interpretable and valuable in the clinic?**

What is "Validation"

- Prefer not use freestanding term "validation"
- Means many things to many people!
- "Analytical validation" fairly well-understood (more later on this) for diagnostic test
- Rather than "clinical validation" --not a very meaningful term--prefer "qualification for use" to reflect the idea that the exercise is quite different depending on what you plan to use the marker for

Considering “Validation”

Three Interrelated Concepts of Validity

- **Biomarker “itself” – there is a real physical state or reality measured by a test: e.g., gene sequence, gene expression, etc.**
- **Genomic test – straightforward to highly complex procedures, & computer algorithms yielding result (s)**
- **Pharmacogenomic test – Results that have meaning (clinical utility) vis-à-vis drug therapy**

Characteristics of Genomic Biomarker "Itself": How much Mechanistic Knowledge Exists?

- **Drug metabolizing enzyme polymorphism**
- **Molecular drug targets**
- **Tissue injury gene expression sequence**
- **Empirically derived correlation pattern**

Mechanistic Knowledge Contributes Support for Marker Validity

- Confidence greater when physiologic, pathophysiologic or pharmacologic link is plausible
- Empirically derived associations have only one line of evidence for the link, and thus require more robust data for that chain of evidence
- Goal is to understand marker in context of disease process—i.e., embedded in a matrix of scientific knowledge and adding to our understanding of clinical medicine

Concept of "Degree of Validity" of Biomarkers

- Refers in principle to physical biomarker, not a specific test for it
- Obviously, specifics of assay are important
- However, "known" or "probable" valid biomarker concept pertains to scientific/medical information about the marker and may encompass a number of assays or ways to do measurement—e.g, clinical chemistry tests, hematocrit, or pulmonary function
- Independence from specific test improves scientific robustness of biomarker

"Qualification" Concept

- Pharmacogenomic biomarker can be used for many purposes
- Animal toxicology
- Early or late drug development—not commercialized for use in healthcare
- Drug development--for use in clinical decision-making and thus required to be commercially available for clinical use

“Qualification” Concept

- Depending on use, type of validation differs
- All tests recommended to achieve reasonable analytical validation
- Safety or other biomarkers not used for clinical decision-making need less certainty
- Biomarkers used to select or reject patients for therapy, etc, need higher certainty
- Surrogate endpoints need highest level of assurance

Genomic Test Analytical Validation

- Are you measuring what you say you are measuring? How are values assigned (+/-)?
- How accurate and reproducible is this measurement? How precise?
- What range of analyte is measurable?
- What sample conditions are acceptable?
- How do you run the test? What are calibrators or controls?
- What interferes with the test?

Genomic Test Analytical Validation

- May perform analytical validation on stored samples
- Desirable to configure test and perform analytical validation prior to employing test in real-time clinical trials
- May need to store “bridging samples” if configuration of test changes during development

Genomic Test Analytical Validation

- Like most diagnostic tests, specification of what result is positive, negative, etc is of great importance
- Traditionally, Receiver-Operating Characteristic Curves have been used to help define cutoffs
- Need for attention and focus on these issues will depend on test characteristics

Further Pharmacogenomic Test "Qualification"

- Distinguish among freestanding tests and test labeled to be used with a drug
- Dependent on amount of pre-existing scientific knowledge on the clinical utility of the result
- Special case of co-development of investigational test and investigational drug

Animal Safety Biomarkers

- Animal testing traditionally used to:
  - Select starting dose
  - Identify potential target organs for toxicity
  - Identify special toxicities poorly tested for in human trials—e.g., reprotox, carcinogenicity

  Identifying new markers to provide more precision and predictability to animal testing not require a high bar.

  Identifying markers to SUBSTITUTE for animal testing much more difficult

Animal Safety Biomarkers

- General goal: develop new genomic markers that improve prediction of organ toxicities
- Additionally: have markers accepted as known valid biomarkers that can be generally used
- Approach: Assess performance (predictive value) in a variety of settings and drug types—make data available to scientific community

Genetic Markers for Metabolism

- Special case since, for many polymorphic enzymes, large body of existing data based on phenotype
- Generally assay approved as “freestanding” test but may refer/utilize specific drug data
- Development of drugs subject to polymorphic metabolism a specific area of interest

Human Safety Biomarkers

- Use of pharmacogenomic biomarkers to provide more sensitive screen for early toxicities in humans highly encouraged
- Use to monitor patients for developing toxicity (e.g., to withhold therapy) will raise the issue of use postmarket—predictive value of test will need to be evaluated

Human Safety Biomarkers

- Initial goal: Develop new genomic biomarkers to use in predicting organ toxicity in trials of investigational agents
- Assess and publish results of biomarker performance in a variety of patient groups and drug classes
- As predictive value becomes understood, develop known valid biomarkers

Human Safety Biomarkers

- Such genomic biomarkers may become promising for general clinical use
- If so, would need to be qualified for such use either as freestanding test or for use with a given drug
- Commercial test configuration would need to be developed

Human Efficacy Biomarkers

- May use to better understand therapeutic effect, help model or refine dose-response, predict time dependency: may not predicate use in clinic
- Use to select patients for treatment, to adjust dose or other decision making would need additional qualification

Consortia: Moving from Probable Valid Biomarker to Known Validity

- Many candidate pharmacogenomic markers exist
- Have performance data within one firm or academic setting; data may or may not be public
- Wider acceptance requires further performance evaluation in multiple hands with a variety of therapeutics
- Biomarker consortia provide ideal setting in which to perform such work

Consortia

- Nonprofit or neutral setting to deal with antitrust and intellectual property issues
- Arrangements for data from “common good” to be put into public domain
- Inventors retain IP rights to individual products
- Need to set up for mutual benefit of drug and device developers and the public

Role of FDA in Consortium Process

- FDA partners in liaison role or through CRADA or other formal mechanism
- FDA provides advice on design of studies that will produce results acceptable for regulatory use
- As needed, FDA will agree to write guidance regarding use of new marker if data are acceptable

Need for Novel Processes

- Current models for general biomarker qualification for use are nonexistent or unsuccessful
- Many (nonpharmacogenomic) markers have been available for decades but their utility in drug development and the clinic still unclear
- Must not be the fate of genomic markers: we must build a robust qualification model

Co-development of Test and Drug

- In many cases, PG test and drug will both be investigational
- In co-development, rely upon clinical phase of drug development program to provide the evidence of clinical utility (i.e., value) of the diagnostic test
- In this case, claim for test would be for use with drug, drug cross-labeled for use with diagnostic
- Other parts of drug and diagnostic development programs (e.g., analytical validation) would proceed as usual

Questions Arising

- Design of trials to accomplish such objectives
- Ability to conduct biomarker identification and qualification in same study
- Issues related to generalizability of results
- Degree to which a study in an enriched population pertains to a broader group
- Questions about approval of a drug in a newly identified subgroup of a larger population

Questions Arising

- Continue to explore these questions in workshop with explicit examples
- FDA goal: draft guidance this year on co-development issues
- Worked examples through VGDS process have been very helpful—need to continue to work through real-world cases

Overall Goals of FDA Pharmacogenomic Initiative

- Critical Path: facilitate the development of more predictive evaluative tools
- Critical Path: improve the path for development of pharmacogenomic assays for use in clinical medicine
- Public Health Mission: facilitate availability of medical products that improve health and therapy outcomes

FDA Partnerships

- Working closely with private sector in collaboration
- Working with other HHS agencies—NIH/NCI and CMS
- Working with standards organizations—NIST in the Federal sector as well as the private sector and nonprofit organizations

Promise Of Pharmacogenomics

- Begin to move therapy from empirical (i.e., trial and error) approach to scientifically based prediction
- Refine definitions of disease
- Ability to avoid certain adverse drug event and therefore improve benefit/risk analysis
- Select patients for therapy based on better predictions of response

Further Importance of "Validation"

- Provide persuasive data on real value of pharmacogenomic tests
- Provide evidence that can be used in cost-effectiveness analysis
- Help payers in decision-making process around reimbursement
- Establish protocols for use in clinical medicine

Summary

- Subject of "validation" of pharmacogenomic assays still requires more discussion and clarity
- Multiple pressing reasons to accomplish this clarity and perform the validations
- Success of these tests in development and in the clinical is dependent on defining achievable and scientifically sound validation pathways